

# Risk factors associated with hantavirus fatality: a regional analysis from a case-control study in Brazil

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## ABSTRACT

**Introduction:** In Brazil, hantavirus cardiopulmonary syndrome (HCPS) has a high lethality rate that varies by region. This study aimed to identify the risk factors associated with fatal hantavirus. **Methods:** This study was a case-control study that included all laboratory confirmed cases of hantavirus. The cases were stratified by the different Brazilian regions using data from the Notifiable Diseases Information System. “Cases” were patients who progressed to death, whereas “controls” were patients who were cured. The odds ratio (OR) and the adjusted OR were calculated. **Results:** Overall, 158 cases and 281 controls were included in this study. In the Midwest region, the cases were 60% less likely to present with flank pain, and the time between the beginning of symptoms and death was shorter than the time between the beginning of symptoms and a cure. In the Southeast region, the cases were 60% less likely to present with thrombocytopenia or reside in rural areas compared to those who progressed to a cure. Additionally, the cases sought medical assistance, notification and investigation more quickly than the controls. In the Southern region, the cases that died were 70% less likely to be male compared to the controls. **Conclusions:** HCPS manifests with nonspecific symptoms, and there are few published studies related to the condition, so determining a patient’s therapeutic strategy is difficult. This study presents findings from different Brazilian regions and highlights the need for further investigations to improve comprehension about regional risk factors associated with hantavirus and to reduce morbimortality.

**Keywords:** Hantavirus infections. Hantavirus syndrome. Brazil. Case-control studies. Risk factors.

## INTRODUCTION

Hantavirus is an emerging zoonosis that is caused by several rodent-borne hantaviruses of the Bunyaviridae family<sup>1</sup>. On the American continent, these viruses are primarily associated with wild rodents of the Cricetidae family, more specifically the Sigmodontinae and Neotominae subfamilies<sup>2,3</sup>. The incubation periods vary from 3 to 60 days, and in nature, the virus is transmitted among rodents when they fight over food or when organisms, including humans, come in contact with contaminated excreta<sup>4</sup>.

In Brazil, hantavirus was first described in 1993 in the municipality of Juquitiba, São Paulo<sup>5</sup>. Since the first cases were observed and technical training for epidemiological investigation was initiated, the disease has been found in new areas, and new genera and variants of hantavirus, as well as additionally species of wild rodents that are involved in the transmission of the virus, have been systematically identified. Hantavirus has been reported in the insectivorous Soricidae and Talpidae families and in bats of the Vespertilionidae and

Nycteridae families; however, hantaviruses have still not been associated with human disease<sup>6-9</sup>.

The most prevalent viral variants of hantavirus are Juquitiba, which occurs in wild rodents living in the Atlantic Forest region; Araraquara, which occurs in wild rodents from the cerrado and caatinga biomes (typical Brazilian vegetation)<sup>10</sup>; Castelo dos Sonhos, which is present in rodents living in the cerrado and Amazon Rainforest; and Anajatuba, which has been found in wild rodents living in the Amazon Rainforest and flooded regions<sup>11</sup>.

In Brazil, hantavirus manifests as hantavirus cardiopulmonary syndrome (HCPS), and the primary symptoms include fever, myalgia, flank and abdominal pain, severe cephalgia, nausea, vomiting and diarrhea; unfortunately, these unspecific symptoms can be confused with many other diseases<sup>11,12</sup>. The most severe symptoms, which begin on approximately the seventh day after the prodromic stage (early disease), primarily consist of a dry cough, tachycardia, tachypnea, hypoxemia, noncardiogenic pulmonary edema, hypotension and circulatory collapse<sup>13</sup>.

According to the Epidemiological Surveillance Guide, during the first week of illness, laboratory confirmed cases of hantavirus present with fever (>38°C), myalgia, cephalgia and respiratory failure of unknown etiology. Additionally, some cases present with an acute disease of unknown etiology that consists of respiratory failure and progresses to death. These individuals often present with fever, myalgia and cephalgia and have been exposed to wild rodents or favorable environmental

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conditions for the existence of wild rodents less than 60 days prior; these patients exhibit IgM serology, positive tissue immunohistochemistry or positive RT-PCR results from the reference laboratory network of the Ministry of Health<sup>11</sup>.

Reporting cases of hantavirus to health services is mandatory in Brazil; however, health services are passively notified, and cases are included in the database of the Notifiable Diseases Information System (SINAN) by the municipal health departments of the regions in which the cases occur. According to data from the hantavirus surveillance system that is managed by the Ministry of Health, 1,606 cases of hantavirus have occurred in Brazil between 1993 and 2012; 25% of these cases occurred in the Midwest, 35.4% occurred in the South and 28% occurred in the Southeast, which corresponds to approximately 88.4% of all of the cases in the country. Most of the cases were male (75%), and 18.8% of the cases had occupations related to agricultural and/or livestock; 24.5% of the cases were between 20-39 years old<sup>14</sup>. During the period from 2007 to 2010, 5,275 suspected cases of hantavirus were reported, of which 538 (10%) were confirmed. The lethality rate ranged from 31.4% in 2007 to 42.6% in 2008.

Due to the high lethality rates and the incipient knowledge about the natural history of hantavirus in Brazil, this study aimed to identify risk factors that are associated with hantavirus fatality in the different regions of the country. For this purpose, a case-control study was performed using secondary data from SINAN that were collected between 2007 and 2010.

## METHODS

This study is a case-control study. The data are secondary and were obtained from SINAN; inconsistencies and duplicate records were deleted prior to the analysis. The variables that were used were present in the individual notification form from the national information surveillance epidemiological system in Brazil between 2007 and 2010, and the entry of these results was standardized. Demographic, epidemiological, clinical, laboratory, hospitalization and treatment variables were used in the analysis. Variables concerning exposures were not used, as our aim was to determine prognostic factors associated with death. This study included every serologically confirmed case of

hantavirus that was registered on SINAN. The authors defined “cases” as patients who died from hantavirus and “controls” as patients who were cured. The numbers of case and control patients did not match, but the analysis was stratified. The odds ratio (OR) was used as the univariate measure of association, and the adjusted OR (AOR) was used as the multivariate measure of association. Statistical significance was set to 5% ( $p \leq 0.05$ ), and 95% confidence intervals were used. For the statistical analysis, the Mann-Whitney U and t tests were used for the continuous variables. Only the variables that demonstrated a significant statistical association with hantavirus fatality are presented. The analysis were performed using the software EpiInfo version 3.5.4.

Because of the different variants of hantavirus that circulate in the different regions of Brazil, the analysis was stratified by region<sup>15</sup>. The Midwest region consists of the Mato Grosso do Sul, Mato Grosso, Goiás and Distrito Federal States. The Southeast region consists of Minas Gerais, Espírito Santo, Rio de Janeiro and São Paulo; and the Southern region contains the Paraná, Santa Catarina and Rio Grande do Sul States. The North and Northeast regions were not included in this analysis because of the low occurrence of hantavirus cases (8 cases and 15 controls in total).

The study was conducted with secondary data and is presented in a collective manner. Nominal information or any other information that could identify each individual was not accessed; therefore, this study did not require the consideration of the ethics committee on research.

## RESULTS

A total of 166 cases and 296 controls were identified in the database. In the Midwest, 72 cases and 104 controls were considered (1:1.4), whereas 48 cases and 84 controls (1:1.7) were included from the Southeast, and 38 cases and 93 controls (1:2.4) were included from the South. The cases and controls were similar in terms of gender, education, ethnicity and age (**Table 1**).

In the Midwest, compared to the controls, the cases were more likely to present with HCPS rather than the prodromic form; to have been hospitalized; and to have presented with signs and symptoms of dyspnea, acute respiratory failure, heart

TABLE 1 - Sociodemographic characteristics of the cases and controls, Brazil, 2007-2010.

Variable	Cases (n=166)		Controls (n=296)		p-value
	n	%	n	%	
Male gender	122	73.5	224	75.7	0.60
Non white ethnicity	57	39.0	99	35.4	0.45
Less than 5 years of education	44	51.2	118	58.7	0.23
	Mean	SD	Mean	SD	p-value
Age	33.5	13.7	33.8	13.1	0.78

SD: standard deviation.

failure, arterial hypertension and pulmonary infiltrates. The cases also had higher odds of receiving vasoactive drugs and mechanical ventilation. However, the patients who died were 60% less likely to have presented with flank pain compared to those who were cured. In the multivariate analysis, flank pain, diffuse pulmonary infiltrates and the use of vasoactive drugs were associated with death. Furthermore, the time between the beginning of symptoms and death was significantly shorter than the time between the beginning of symptoms and a cure (**Table 2**).

In the Southeast, the cases were more likely to have presented with hypovolemic shock, hypotension and acute respiratory failure. Furthermore, compared to the controls, there were increased levels of leukocytes with a shift to the left and the increased use of vasoactive drugs and mechanical ventilation. Nevertheless, the cases of hantavirus that progressed to death were 70% less likely to live in rural areas or present with headaches and thrombocytopenia compared to the patients who progressed to a cure. A logistic regression analysis showed that thrombocytopenia and the use of mechanical ventilation were associated with the cases. Furthermore, the first medical assistance, notification, investigation and the course of the disease occurred more quickly in the cases than in the controls (**Table 3**).

In the South, death was significantly associated with clinical manifestations related to HCPS, hypovolemic shock, respiratory and cardiac failure, dyspnea, hypotension, pleural effusion, hematocrit greater than 45%, pulmonary infiltrates and the use

of vasoactive drugs and mechanical ventilation. As in the other regions, the time between the beginning of symptoms and death was significantly shorter than the time between the beginning of symptoms and a cure, and the time between the beginning of symptoms and disease notification was significantly shorter for the cases. Patients who progressed to death were 60% less likely to be male than patients who were cured. In the adjusted analysis, shock, the use of vasoactive drugs and being male remained statistically significant (**Table 4**).

## DISCUSSION

Despite the low incidence in Brazil, hantavirus manifests as a severe illness. The limited amount of scientific literature on the topic hampers the decision-making process concerning patient care in some situations, as there are limited profiles of disease occurrence and there is limited evidence related to the disease. The risk factors for contracting hantavirus are known<sup>11</sup>. This study provides important new information on the risk factors associated with death from hantavirus, demonstrating the differences in the Brazilian regions. While we know there are other risk factors associated with death from hantavirus, we only analyzed parameters that were present in the SINAN database. For example, this study found that the odds of dying from hantavirus in the Southern region were the lowest among men, whereas in the Southeast region, the odds of dying from hantavirus were the lowest among people living in rural areas, which is the typical profile of affected individuals<sup>11</sup>. These

TABLE 2 - Variables associated with hantavirus fatality in the Midwest region of Brazil, 2007-2010.

Variable	Cases (n=72)		Controls (n=104)		OR (95% CI)	AOR (95% CI)
	n	%	n	%		
<b>Clinical presentation</b>						
HCPS	68	94.4	70	67.3	8.3 (2.8-24.5)	3.3 (0.2-68.3)
flank pain	15	25.9	46	49.5	0.4 (0.2-0.7)	0.1 (0.03-0.8)
hypotension	42	64.6	28	31.1	4.0 (2.1-7.9)	7.1 (0.9-54.1)
dyspnea	65	92.6	76	74.5	4.4 (1.6-12.2)	2.2 (0.1-39.1)
heart failure	9	15.8	3	3.4	5.2 (1.4-20.3)	0.1 (0.1-2.43)
acute respiratory failure	47	71.2	28	30.1	5.7 (2.9-11.5)	1.6 (0.3-8.2)
<b>Laboratory findings</b>						
diffuse pulmonary infiltrates	52	94.5	49	72.1	6.7 (1.9-24.1)	25.5 (1.2-547.1)
<b>Therapeutic Treatment</b>						
vasoactive drugs	41	70.7	14	23.7	7.8 (3.4-17.7)	19.5 (1.7-225.6)
mechanical ventilation	45	70.3	29	36.7	4.1 (2.0-8.3)	0.8 (0.1-8.1)
Time (interval in days)	Mean	SD	Mean	SD	p-value	
Course of the disease	6.0	5.1	17.3	12.8	<0.05	

HCPS: hantavirus cardiopulmonary syndrome; SD: standard deviation; OR: odds ratio; AOR: adjusted OR. CI: confidence interval.

TABLE 3 - Variables associated with hantavirus fatality in the Southern region of Brazil, 2007-2010.

Variable	Cases (n=48)		Controls (n=84)		OR (95% CI)	AOR (95% CI)
	n	%	n	%		
<b>Socio-demographic</b>						
residence in rural areas	4	9.3	21	25.6	0.3 (0.1-0.9)	5.2 (0.5-52.9)
<b>Clinical presentation</b>						
headache	23	54.8	62	14.7	0.4 (0.2-0.9)	0.5 (0.1-3.2)
hypotension	27	65.9	27	35.1	3.6 (1.6-7.9)	1.8 (0.2-16.8)
hypovolemic shock	28	63.6	7	8.9	18.0 (6.7-48.4)	7.2 (1.0-53.0)
<b>Laboratory findings</b>						
increased levels of leukocytes with a shift to the left	20	41.7	20	23.8	2.3 (1.1-4.9)	0.6 (0.1-4.0)
thrombocytopenia	17	51.5	41	74.5	0.4 (0.1-0.9)	0.1 (0.01-0.7)
<b>Therapeutic Treatment</b>						
vasoactive drugs	30	71.4	12	19.4	10.4 (4.1-26.1)	0.7 (0.05-10.8)
mechanical ventilation	39	88.6	18	26.5	21.7 (7.4-63.5)	11.1 (1.4-87.1)
<b>Time (interval in days)</b>						
	Mean	SD	Mean	SD	p-value	
Beginning of symptoms and medical assistance	2.2	2.8	4.0	4.9	<0.05	
Course of the disease	7.7	12.5	18.6	15.0	<0.05	
Beginning of symptoms and investigation	6.1	10.8	14.4	39.3	<0.05	
Beginning of symptoms and notification	6.1	10.8	13.6	39.0	<0.05	

SD: standard deviation. OR: odds ratio; AOR: adjusted OR. CI: confidence interval.

TABLE 4 - Variables associated with hantavirus fatality in the Southern region of Brazil, 2007-2010.

Variable	Cases (n=38)		Controls (n=93)		OR (95% CI)	AOR (95% CI)
	n	%	n	%		
<b>Socio-demographic variable</b>						
male gender	26	68.4	79	84.9	0.4 (0.2-0.9)	0.3 (0.003-0.3)
<b>Clinical presentation</b>						
HCPS	31	81.6	58	62.4	2.7 (1.1-6.7)	1.0 (0.1-7.3)
dyspnea	35	92.1	66	71.0	4.8 (1.3-16.8)	1.2 (0.1-22.8)
hypotension	23	62.2	34	37.0	2.8 (1.3-6.1)	1.5 (0.2-10.8)
acute respiratory failure	33	86.8	40	43.5	8.6 (3.1-24.0)	2.8 (0.3-30.1)
heart failure	8	22.2	6	6.7	4.0 (1.3-12.5)	4.6 (0.3-70.7)
hypovolemic shock	22	59.5	7	7.7	17.6 (6.4-48.4)	10.2 (1.3-77.5)
<b>Laboratory findings</b>						
hematocrit >45%	25	80.6	46	55.4	3.3 (1.2-9.0)	8.6 (0.7-100.6)
diffuse pulmonary infiltrates	26	83.9	40	5.6	4.2 (1.4-12.1)	2.4 (0.2-23.7)
<b>Therapeutic Treatment</b>						
vasoactive drugs	23	62.2	18	22.2	5.7 (2.4-13.4)	1.8 (0.2-12.8)
mechanical ventilation	27	73.0	22	26.8	7.4 (3.1-17.7)	10.2 (1.0-103.1)
<b>Time (interval in days)</b>						
	Mean	SD	Mean	SD	p-value	
Course of the disease	9.6	15.1	15.9	10.3	<0.05	
Beginning of symptoms and notification	8.1	13.9	9.5	9.9	<0.05	

HCPS: hantavirus cardiopulmonary syndrome; SD: standard deviation; OR: odds ratio; AOR: adjusted OR; CI: confidence interval.

differences are most likely related to regional differences in who receives more and appropriate attention at the time of patient care. For example, patients with hantaviruses require treatment that is designed for hantaviruses rather than for other diseases with similar symptoms, such as dengue. A recent study performed in the State of Ceará found anti-hantavirus antibody titers in patients suspected of having dengue<sup>16</sup>, which demonstrates the need to strengthen the differential diagnosis to provide a clinical-epidemiological approach at the time of suspicion. Because of the nonspecific signs and symptoms associated with hantaviruses, which are easily confused with other diseases, appropriate supportive treatment (there is no specific treatment) is necessary to control the lethality rate of hantaviruses<sup>13</sup>.

When analyzing the course of the disease between the beginning of symptoms and either cure or death, those who progressed to death generally did so in a third of the time as those who progressed to a cure. These results may be due to the movement of the different hantavirus variants that have been registered and isolated from human cases in Brazilian regions<sup>15</sup>. However, more detailed studies are needed to determine the mechanisms of infection and immune response, the pathogenicity and diagnostic potential of the variants and the appropriate supportive treatment for the disease.

The symptoms and laboratory findings related to death were clearly related to the severity and evolution of the cases. The notification form from the SINAN was not designed to monitor the patient's evolution, and there was only one registration for each patient. Because we gathered our data from this information system, the registration of symptoms can be a predictor or a consequence of other conditions, but at the time of the investigation, the included patients were registered and presented as having hantaviruses. However, a study conducted with the same data but with a focus on the prognostic factors for hantavirus fatality found that respiratory distress syndrome (RDS) and the need for mechanical respiratory assistance were also associated with death. When these variables were excluded from the model, dyspnea and hemoconcentration were associated with an increased risk of death<sup>18-20</sup>. We did not use the same exclusion in our study; however, we identified factors that could aid in the prognosis of death, such as thrombocytopenia.

This study aimed to present epidemiological evidence that may support other studies concerning the progression of hantaviruses, especially regional studies that consider the variant forms of the virus, the means of exposure to the disease, the evolution of the disease and access to medical assistance. This study will contribute to health education actions and provide scientific evidence for medical personnel.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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